

# Obstetrical and Pediatric Anesthesia

## Psychiatric side effects of indomethacin in parturients

*[Les effets secondaires psychiatriques de l'indométhacine chez les parturientes]*

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**Purpose:** To examine the central nervous system side effects of the non-steroidal anti-inflammatory drug (NSAID) indomethacin in a case-series of obstetric patients.

**Methods:** The hospital records of patients experiencing any postpartum complication between 1994 and 1999 were reviewed for adverse drug reactions (ADR) attributed to indomethacin. Additional cases of indomethacin-induced adverse effects were identified through reports to the nursing administration and the Saskatchewan ADR reporting program. The Naranjo ADR probability scale was applied to all cases.

**Results:** Thirty-two patients experienced a psychiatric reaction after receiving indomethacin for postpartum pain. The symptoms were often severe and included dizziness, anxiety, fear, agitation, affective lability, depersonalization, paranoia, and hallucinations. There was no past psychiatric history documented in any of the cases.

**Conclusion:** This study identifies a possible ADR to indomethacin occurring in postpartum patients. Whether the vulnerability to these neuropsychiatric reactions is randomly distributed or if parturients are at increased risk is yet to be determined. Proposed mechanisms of these side effects include a postpartum dopamine supersensitivity exacerbated by prostaglandin inhibition as well as a structural similarity between serotonin and indomethacin. The severity of the reactions to indomethacin in parturients and the potential for these disturbing psychiatric side effects to compromise the safety of both mother and infant have led to the use of alternative analgesics including different classes of NSAIDs for this population at our institution.

**Objectif:** Vérifier les effets secondaires centraux d'un anti-inflammatoire non stéroïdien (AINS), l'indométhacine, dans une série de cas d'obstétrique.

**Méthode :** Nous avons passé en revue les dossiers hospitaliers des patientes qui avaient subi des complications postpartum causées par des effets indésirables des médicaments (EIM), en l'occurrence l'in-

dométhacine, entre 1994 et 1999. D'autres cas reliés à l'indométhacine provenaient de déclaration faite à l'administration des soins infirmiers et au programme de déclaration des EIM de la Saskatchewan. L'échelle de probabilité d'EIM de Naranjo (Naranjo ADR probability scale) a été appliquée à tous les cas.

**Résultats :** Trente-deux patientes ont subi une réaction psychiatrique à l'indométhacine reçue pour la douleur du postpartum. Les symptômes, souvent sévères, comprenaient : étourdissements, anxiété, crainte, agitation, labilité de l'affect, dépersonnalisation, paranoïa et hallucinations. Aucune de ces femmes n'avait d'antécédents psychiatriques.

**Conclusion :** L'étude montre un EIM possible de l'indométhacine chez des patientes en postpartum. Il reste à déterminer si la vulnérabilité à ces effets neuropsychiatriques est aléatoirement distribuée ou si les parturientes sont plus à risque. On croit que ces effets secondaires pourraient relever d'une hypersensibilité postpartum à la dopamine, qui serait exacerbée par l'inhibition de prostaglandine, ou d'une similarité structurelle entre la sérotonine et l'indométhacine. La sévérité des réactions à l'indométhacine chez les parturientes et leur potentiel de compromettre la sécurité de la mère et de l'enfant ont incité à utiliser d'autres analgésiques, y compris les différentes classes d'AINS, pour cette catégorie de patientes à notre institution.

**T**HIS study investigates the observations made by nurses of bizarre psychiatric symptoms occurring in parturients after receiving indomethacin for postpartum pain. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) used either alone or as an adjuvant analgesic in many acute and chronic pain states including the puerperium.<sup>1</sup> Central nervous system (CNS) side effects of NSAIDs are often unappreciated, under-reported and overshadowed by the gastroin-

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TABLE I Naranjo adverse drug reactions (ADR) probability scale criteria<sup>7</sup>

Questions	Yes	No	Don't know
1) Are there previous conclusive reports on this reaction?	+1	0	0
2) Did the ADR appear after the suspected drug was administered?	+2	-1	0
3) Did the ADR improve when the drug was discontinued?	+1	0	0
4) Did the ADR appear with re-challenge?	+2	-1	0
5) Are there alternative causes for the ADR?	-1	+2	0
6) Did the reaction appear when placebo was given?	1	+1	0
7) Was the drug detected in blood at toxic levels?	+1	0	0
8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9) Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10) Was the ADR confirmed by any objective evidence?	+1	0	0

TABLE II Central nervous system (CNS) side effects of indomethacin described in hospital records of parturients

CNS side effect	Number of parturients experiencing side effect
Dizziness	23
Agitation	12
Anxiety	12
Fear	9
Dyspnea	8
Dysphoria	7
Depersonalization	4
Panic	4
Fear of dying	4
Hallucinations	4
Abnormal movements	2

testinal, antiplatelet and renal effects of these structurally diverse drugs.<sup>2</sup> Although the true incidence of psychiatric reactions related to NSAID use remains unknown, there have been more than 20 published case reports of NSAID-induced psychosis.<sup>2-6</sup>

### Methods

A retrospective study of neuropsychiatric reactions following indomethacin administration in parturients was conducted at our institution. Cases were identified by reviewing the hospital records of patients experiencing any postpartum complication between August 1, 1994 and July 31, 1999. Additional cases were identified for that same time period through reports to the Saskatchewan adverse drug reaction (ADR) reporting program. All cases were temporally related to the indomethacin dose and documented in the chart as an indomethacin side effect by the nurse, physician and/or pharmacist.

Data collected from all of the reviewed charts included: demographic data; mode of delivery; method of labour analgesia; indomethacin dose; time and route of administration; a description of the ADR; medication history; known drug allergies and past psychiatric history.

The Naranjo ADR probability scale is a tool used to determine the likelihood that an ADR is caused by the implicated medication.<sup>7</sup> Ten questions are answered and assigned a weighted score of +2 to -2. Where there is insufficient data available, the particular question receives a 0. Based on the Naranjo criteria (Table I) each case is scored (< 1 - > 9) and assessed a likelihood of causing an ADR from doubtful, possible, probable to highly probable. The Naranjo probability scale was applied by one individual to all suspected cases of indomethacin-induced neuropsychiatric reactions.

### Results

Thirty-two women experienced adverse psychiatric reactions after receiving indomethacin for postpartum analgesia. Twelve of the cases had been reported to the Saskatchewan ADR reporting program. The symptoms were often severe and included dizziness, anxiety, fear, agitation, affective lability, depersonalization, paranoia and hallucinations (Table II).

The average age of the parturients experiencing the ADR was 31 yr. The mode of delivery was a Cesarean delivery in 22 patients and a vaginal delivery in ten cases. The indomethacin dose and route of administration most frequently associated with the ADR was 100 mg rectal suppository in 30 of the 32 cases. The remaining two patients experienced side effects after a 50 mg rectal suppository. Whether this reflects a dose response is not clear as 100 mg suppositories were more commonly prescribed. The side effects were most often reported to occur within one hour of

receiving indomethacin with the duration of symptoms recorded in 24 cases as less than six hours. The remainder of the charts did not note duration of ADR. More than one dose of indomethacin was administered to 13 of the 32 parturients before the psychiatric symptoms were documented. Benzodiazepines were administered short-term to relieve symptoms in six cases. There was no past psychiatric history documented in any of the cases.

The reactions depicted in the charts were strikingly similar with symptoms of panic frequently described. In one patient's chart the nurse wrote, "*patient complaining of feeling very panicky. Does not want to handle the baby...crying uncontrollably, states she lost control after the Indocid suppository-feels worse than labour*". Another chart reads "*one hour after the Indocid suppository patient became very agitated and fearful - wanted nurse present constantly. Panicky, afraid she will lose control. Paranoid - very watchful and suspicious. Delayed responses to questions*".

The Naranjo scores ranged from 0 to 8 with the majority of the cases (30/32) being assigned a likelihood score of possible. The retrospective nature of the study limited the application of the Naranjo scale as many of the questions regarding previous exposure, re-challenge and placebo response went unanswered and therefore received a score of 0.

### Discussion

NSAID-induced CNS side effects have previously been described predominantly in the elderly, with indomethacin the most frequently reported NSAID to produce psychiatric reactions.<sup>2</sup> Whether the vulnerability to these neuropsychiatric reactions is randomly distributed or if parturients are at increased risk is yet to be determined. Proposed mechanisms of these side effects include a postpartum dopamine supersensitivity exacerbated by prostaglandin inhibition<sup>9,10</sup> as well as a structural similarity between serotonin and indomethacin.<sup>2</sup> The range of activities of different NSAIDs with respect to the cyclooxygenase 1 (COX-1) compared to COX-2 enzyme may also explain some variations in side effect profiles.

Although a temporal relationship exists between adverse psychiatric side effects and NSAIDs, there are difficulties inherent in determining a cause and effect relationship between any drug and a specific side effect.<sup>3</sup> These difficulties are magnified when the ADRs consist entirely of subjective complaints in a postpartum population already vulnerable to mood swings and postpartum blues. The difficulties encountered in this investigation in identifying ADRs consequent to reporting and poor documentation highlight the need for

enhanced drug surveillance programs and diligent reporting of all ADRs. The retrospective nature of the investigation and the unknown incidence of this potential side effect in the parturient population further limit this study. Nevertheless the psychiatric symptoms occurring after indomethacin administration were sufficiently dramatic and disruptive to patient and infant care to imply that the association exists. The potential for these severe indomethacin-induced psychiatric reactions to compromise the safety of both mother and infant have led to the use of alternative analgesics including different classes of NSAIDs for this population at our institution.

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